UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,892	02/09/2007	David S. Lawrence	96700/1160	1824

1912 7590 12/28/2009

AMSTER, ROTHSTEIN & EBENSTEIN LLP
90 PARK AVENUE
NEW YORK, NY 10016

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
12/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,892	LAWRENCE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *5,7,8,22,23,26,32-34 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,9-21,24,25,27-31,35,36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/20/2006; 4/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 are pending in the instant application.

Election/Restrictions

Applicant's election without traverse of gentamicin as the species of agent effective to suppress a mutation/correct a defect caused by a mutation, and thioguanine as the species of agent effective to increase transcription of a gene in the reply filed on 4/13/2009 is acknowledged.

The reply filed 4/13/2009 indicates that all claims are readable on the elections with the exceptions of claims 5, 7-8, 22-23, 26, 32-34 and 37.

Claims 5, 7-8, 22-23, 26, 32-34 and 37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/13/2009.

An examination on the merits of claims 1-4, 6, 9-21, 24-25, 27-31, 35-36 and 38 follows.

Information Disclosure Statement

Receipt of information disclosure statements, filed on 4/13/2009 and 7/20/2006, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

Specification

The use of the trademarks QUIKCHANGE (paragraph [0030]); GENEJAMMER (paragraph [0032]); DUAL LUCIFERASE (paragraph [0033]); TRIZOL (paragraph [0035]); and

PRIMER EXPRESS (paragraph [0035]) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31, 35-36 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites the limitation "the gene" in line 5. There is insufficient antecedent basis for this limitation in the claim. Although the claims make reference to a protein disrupted by a genetic mutation, the method is performed in a subject that comprises genes other than the gene encoding the protein disrupted by a genetic mutation. Thus, it is unclear if "the gene" is referring to an element already present in the claim or another gene. The metes and bounds of "the gene" are unclear.

Claims 35-36 and 38 depend from claim 31 and are rejected for the same reason applied to claim 31.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 9-21, 24-25, 27-31, 35-36 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating ataxia telangiectasia in a subject, comprising administering to the subject an amount of gentamicin effective to suppress a premature stop codon in the *atm* gene, and an amount of a fluorinated quinolone or thioguanine effective to increase transcription of the *atm* gene, does not reasonably provide enablement for making and using an agent effective to increase transcription of any gene disrupted by the presence of a premature stop codon, and making and using the method to enhance production of a protein disrupted by any genetic mutation where a compound is administered to suppress the genetic mutation and/or correct a defect caused by the mutation, and a compound is administered to increase transcription of the gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claims 1-4, 6, 9-21, 24-25 and 27-30 are drawn to a method for enhancing production in a subject of a functional protein from a gene disrupted by the presence of a premature stop codon in the coding region of the gene, comprising administering to the

subject an amount of an agent effective to suppress the premature stop codon and an amount of an agent effective to increase the transcription of the gene. Dependent claims limit the agent effective to suppress the premature stop codon to an aminoglycoside antibiotic (claim 2) or gentamicin (elected species, claims 3 and 4). The dependent claims limit the agent that increases transcription of the gene to an agent that activates a promoter of the gene (claim 6), or more specifically thioguanine (claim 9). Dependent claims 10-16 are directed to the level of enhancement obtained by the agents. Claim 17 requires the agent that suppresses the premature stop codon to be administered at a dose lower than the dose that would be required to produce the same amount of functional protein in the absence of the agent that increases transcription. Claim 18 requires the lower dose of claim 17 to result in decreased toxicity. Claims 19-21 require the disruption of the gene to be associated with a genetic disorder (claim 19), a genetic disorder selected from the group consisting of thalassemia, hemophilia A, hemophilia B, von Willebrand's disease, a p53 related cancer or disorder, a colorectal cancer, cystinosis, cystic fibrosis, Duchenne muscular dystrophy, Tay-Sachs disease, Wilms tumor, retinoblastoma, neurofibromatosis, ataxia telangiectasia, Hurler's syndrome, mucopolysaccharidosis I, and late infantile neuronal ceroid lipofuscinosis (claim 20), or ataxia telangiectasia (claim 21). Claim 24 limits the agent that activates the promoter of the gene mutated in ataxia telangiectasia to thioguanine. Claim 25 limits the agent that suppresses a stop codon in ataxia telangiectasia to gentamicin. Claim 27 requires the genetic disorder to be treated. Claim 28 requires the disrupted gene to be a tumor suppressor gene, and claim 29 limits the tumor suppressor gene to BRCA1, BRCA2, PTEN, NF1, NF2, MLH1, MLH2, VHL, WT1, TSC1, TSC2 and/or ATM.

Claim 30 requires enhanced production of the functional protein to be effective in treating a tumor in a subject.

The nature of the invention is complex in that one must know how to make and use compounds that activate expression of a gene disrupted by a premature stop codon, including any gene that is associated with a genetic disorder, any gene associated with the specific genetic disorders recited in the claims, any tumor suppressor gene, and any tumor suppressor gene recited in the claims. The expression activators must also be capable of acting on the promoter of the gene disrupted by a premature stop codon.

Claims 31, 35-36 and 38 are drawn to a method for enhancing the production in a subject of a functional protein, where production of the protein is disrupted by a genetic mutation, comprising administering to the subject an amount o f an agent effective to suppress the genetic mutation and/or correct a defect caused by the mutation, and an amount of an agent effective to increase transcription of a gene. Claim 35 requires the agent that increases transcription of the gene to be an agent that activates a promoter of the gene. Claim 36 requires the genetic mutation be associated with a genetic disorder, and claim 38 requires the treatment of the genetic disorder.

The nature of the invention is complex in that one must know how to make and use compounds that can suppress and/or correct any type of genetic mutation (e.g., nonsense, missense, frame shift, exon skipping, insertion, deletion, gross genomic rearrangement), and one must know how to make and use compounds that increase the transcription of a gene.

Breadth of the claims: The claims are broad in that they encompass the use of compounds of any structure effective to enhance production of a functional protein that is disrupted by any type of genetic mutation. Further, the claims broadly encompass the treatment of any genetic

disorder. Moreover, the claims encompass the use of any agent that increases transcription of any gene. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches that the termination of protein synthesis is signaled by the nucleic acid stop (nonsense) codons UAA, UAG, and UGA, and nonsense mutations occur when a sense codon is changes into one of the three stop codons (e.g., paragraph [0005]). Nonsense mutations result in the premature termination of protein synthesis, and the truncation or absence of a key protein product and are associated with a host of genetic diseases, including thalassemia (α-globin and β-globin genes), hemophilia A and B (factor VIII and factor IX genes), von Willebrand's disease (vWF gene), p53 related cancers (p53 gene), colorectal cancers *(APC,* MSH1, and MSHZ genes), cystic fibrosis (CFTR gene), Duchenne muscular dystrophy (dystrophin gene), Tay-Sachs disease (hexosaminidase A gene), Wilms tumor (Wtl gene), retinoblastoma (Rb gene), neurofibromatosis (IW1 and NFZ genes), ataxia telangiectasia *(atnz* gene), the lysosomal storage disease mucopolysaccharidosis I (IDUA gene), Hurler's syndrome, cystinosis, and late infantile neuronal ceroid lipofuscinosis. Alternatively, the nonsense mutation can occur in a tumor suppressor gene, such as BRCA1, BRCA2, PTEN, NF1, NF2, MLH1, MLH2, VHL, WTI, TSCl, TSC2, and ATM (e.g., paragraph [0023]).

The specification teaches that it was known in the art that gentamicin and other aminoglycoside antibiotics can suppress premature stop codon arrest by inducing the ribosome to read past the nonsense mutation via insertion of a random amino acid by a noncognate tRNA (e.g., paragraph [0006]). The specification acknowledges that the prior art teaches the use of

aminoglycosides to suppress nonsense mutations in human cell lines and animal models of Hurler's syndrome, Duchenne muscular dystrophy, late infantile neuronal ceroid lipofuscinosis, cystinosis, cystic fibrosis, mucopolysaccharidosis I, and P863 gene related disorders (e.g., paragraph [0006]). Moreover, gentamicin has also been used in patients with cystic fibrosis and Duchenne muscular dystrophy (e.g., paragraphs [0006] and [0013]).

With regard to the compound used to suppress a premature stop codon, the specification teaches the use of an aminoglycoside antibiotic, or PTC124 (e.g., paragraph [0012]). Aminoglycoside antibiotics include gentamicin, geneticin, paromomycin, hygromycin, G-418, kanamycin, anlikacin and tobrarnycin (e.g., paragraph [0012]).

The specification envisions the suppression of mutations other than nonsense mutations. The specification envisions the suppression and/or correction of mutations such as exon skipping mutations, missense mutations, and frameshift mutations resulting from insertions or deletions (e.g., paragraph [0025]). The specification asserts that agents that suppress exon skipping mutations and/or correct the defect caused by the mutation are "hybrid peptide-nucleic acid molecules (Cartegni and Krainer, 2003), a 2'-*O*-methyl phosphorothioate oligonucleotide combining an antisense sequence and an exonic splicing enhancer sequence (Skordis et al., 2003), sodium butyrate (Chang et al., 2001), and the anthracycline aclarubicin (Andreassi et al., 2001)" (paragraph [0026]). The cited references have been made of record in the IDS filed 4/13/2009.

The specification envisions using an agent that increases transcription of a gene, such as an agent that activates a promoter of a gene (e.g., paragraph [0014]). The specification envisions the use of agents that directly or indirectly activate a promoter (e.g., paragraph [0014]). The

specification states that activators can be identified by one skilled in the art using methods similar to those disclosed in the specification (e.g., paragraph [0015]). For example, the specification envisions the identification of activators by (i) cloning the promoter of the gene; (ii) attaching the promoter to a luciferase cDNA; (iii) transfecting the promoter/luciferase construct into an appropriate cell line; and (iv) using the cell line to simultaneously screen multiple candidate activators of the promoter (e.g., paragraph [0015]). The specification envisions screening a library of nearly 400 drugs approved by the Federal Drug Administration (FDA) (e.g., paragraph [0015]).

The working examples teach the application of the abovementioned screening assay for agents that increase transcription of a gene to the *atm* gene, which is mutated in ataxia telangiectasia. The specification notes that high glucose levels up-regulate ATM message and protein levels (e.g., paragraph [0037]). With regard to the compounds identified by the assay, the specification states, "several FDA approved drugs activate the *atm* promoter, including the fluorinated quinolone ofloxacin" (paragraph [0037]). The specification teaches that fluorinated quinolones are known to target eukaryotic topoisomerase II, an enzyme that catalyzes the interpenetration of DNA strands by introducing transient double strand breaks, and the possible mechanism by which ofloxacin activates the *atm* promoter is via the induction of double strand break recognition or repair (e.g., paragraph [0037]). The specification notes that if this mechanism is correct, then the production of ATM protein would need to be sufficient to offset any drug-induced double strand breaks (e.g., paragraph [0037]). The specification also discloses that the antimetabolite thioguanine also increases *atm* promoter activity (e.g., paragraph [0037]). The specification alludes to other compounds that induce *atm* promoter activity but does not

disclose the compounds by name or structure. The effects of ofloxacin; geneticin; gentamicin; ofloxacin and gentamicin; thioguanine and gentamicin; and ofloxacin and geneticin were studied in a cell culture model. Each of the compound(s) tested increased the expression of functional protein from the coding sequence linked to an *atm* promoter. The effects of the compounds appear to be specific to the *atm* promoter. The specification does not provide evidence that the actions of ofloxacin and thioguanine can be extrapolated to the promoter of any gene that contains a mutation.

Predictability and state of the art: At the time the invention was made, the delivery of agents effective to suppress a genetic mutation and/or correct a defect caused by the mutation and/or agents that increase transcription of a gene across the blood-brain barrier was underdeveloped. With regard to the correction of exon-skipping mutations with oligonucleotides, Cartegni and Krainer (Nature Structural Biology, Vol. 10, No. 2, pages 120-125, February 2003, cited on the IDS filed 4/13/2009 and at paragraph [0125] of the specification) and Skordis et al (PNAS, USA, Vol. 100, No. 7, pages 4114-4119, April 2003, cited on the IDS filed 4/13/2009 and at paragraph [0125] of the specification) teach how to make reagents that increase amount of transcript with the normally skipped exon present. However, Skordis et al teach that the systemic administration of oligonucleotides to correct exon skipping might not be successful in clinical applications because of their inability to cross the blood-brain barrier (e.g., page 4119, paragraph bridging columns). Skordis et al teach the ability to cross the blood-brain barrier will be of great importance in terms of therapeutic possibilities for patients with SMA (e.g., page 4119, paragraph bridging columns). This will hold true for any disease where the pathophsiology of the disease involves the brain (e.g., Tay-Sachs disease). While the

specification envisions using 2'-*O*-methyl phosphorothioate oligonucleotides, Godfray et al (Expert Opinion on Therapeutic Targets, Vol. 7, No. 3, pages 363-376, June 2003) teach that these oligonucleotides do not cross the blood-brain barrier and have not been demonstrated to be effective in the brain (e.g., page 364, right column, last paragraph). Parekh-Olmedo et al (Gene Therapy, Vol. 12, pages 639-646, 2005, cited on the IDS filed 7/20/2006) teach that oligonucleotide delivery must be optimized before targeted gene repair is considered useful for clinical applications and that animal models must be tested to validate the overall approach (page 639, In brief). Furthermore, Hu et al (Current Opinion in Allergy and Clinical Immunology, Vol. 8, No. 6, pages 540-546, December 2008, printed as pages 1/11 to 11/11) teach that most antibiotics do not cross the blood-brain barrier efficiently and would be of limited use for treating central nervous system diseases (e.g., page 3 of 11, 2nd full paragraph).

The state of the art regarding compounds effective to increase transcription of any gene associated with a genetic disease or any tumor suppressor gene was underdeveloped at the time the invention was made. Neither the specification nor prior art of record teach the structures of the compounds that are capable of increasing the transcription of genes associated with thalassemia (α-globin and β-globin genes), hemophilia A and B (factor VIII and factor IX genes), von Willebrand's disease (vWF gene), p53 related cancers (p53 gene), colorectal cancers *(APC,* MSH1, and MSHZ genes), cystic fibrosis (CFTR gene), Duchenne muscular dystrophy (dystrophin gene), Tay-Sachs disease (hexosaminidase A gene), Wilms tumor (Wtl gene), retinoblastoma (Rb gene), neurofibromatosis (IW1 and NFZ genes), ataxia telangiectasia *(atnz* gene), the lysosomal storage disease mucopolysaccharidosis I (IDUA gene), Hurler's syndrome, cystinosis, and late infantile neuronal ceroid lipofuscinosis, or with tumor suppressor genes, such

as BRCA1, BRCA2, PTEN, NF1, NF2, MLH1, MLH2, VHL, WTI, TSCl, TSC2, and ATM. It would have been unpredictable to make and use compounds without defined chemical structure.

Amount of experimentation necessary: It would require a large amount of experimentation to overcome the art-recognized obstacles of drug delivery across the blood brain barrier to increase production of a functional expression from a gene for the treatment of any disease involving the central nervous system. Furthermore, the claims encompass a genus of compounds defined only by their function (i.e., to increase transcription of a gene), wherein the relationship between the structural features of the members of the genus and the function have not been defined, except for ofloxacin and thioguanine for increased expression of the *atm* gene. In the absence of a structural-functional relationship, either disclosed in the as-filed specification or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the disclosed assay does not overcome this defect since one would have not knowledge beforehand as to whether or not any given compound for any given gene (other than ofloxacin and thioguanine for increased expression of the *atm* gene) would fall within the scope of what is claimed. It would require undue experimentation to randomly screen undefined compounds for the claimed activity.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims

1-4, 6, 9-21, 24-25, 27-31, 35-36 and 38 are not considered to be fully enabled by the instant specification.

Claims 1-4, 6, 10-21, 25, 27-31, 35, 36 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require the provision of a genus of agents effective to increase transcription of a gene. The claims also require a genus of agents that directly or indirectly activate a promoter of a gene. The rejected claims thus comprise a genus of agents that are defined by function.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes the reduction to practice of ofloxacin, a fluorinated quinalone, and thioguanine for the *atm* gene (e.g., Examples). There are no drawings or structural formulas disclosed of any other agents that increase the expression of the atm gene or any other gene encompassed by the claims. The specification describes a method of screening compounds for the ability to increase expression by acting on a promoter of a gene (e.g., Examples). However, there is no information regarding what structural features would likely be associated with the increased expression of each of the genes encompassed by the claims. The

specification does not disclose a correlation between increased expression and the structure of an agent. The specification discloses that ofloxacin likely acts to increase *atm* gene expression by introducing double strand breaks, which is consistent with the role of ATM in DNA double strand break recognition and/or repair (e.g., paragraph [0037]). Thus, the action of ofloxacin on the *atm* gene promoter is not likely to be extrapolated to the genus of promoters encompassed by the claims.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of fluorinated quinolones (such as ofloxacin), and thioguanine for activation of the *atm* gene promoter. The results are not necessarily predictive of other compounds that act on the *atm* gene promoter. For example, ofloxacin is a fluorinated quinolone, while thioguanine is an antimetabolite (e.g., paragraph [0037]). The specification does not disclose other structures capable of activating the *atm* gene promoter or the promoters of other genes. Thus, it is impossible for one to extrapolate from the examples described herein those agents that would necessarily meet the structural/functional characteristics of the rejected claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of agents, and therefore conception is not achieved

until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

Given the very large genus of agents encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the structures capable of increasing the expression of the genes encompassed by the claims, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus. There is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those agents that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 1-4, 6, 10-21, 25, 27-31, 35, 36 and 38.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6, 10-16, 19-21, 27-31, 35-36 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Wilde et al (US Patent Application Publication No. 2004/0067900 A1, cited in a prior action; see the entire reference).

Regarding claims 1, 6, 10-16, 19-21, 27-31, 35-36 and 38, Wilde et al teach a method of treating ataxia telangiectasia in a subject, comprising administering to the subject an amount of an agent of the invention effective to suppress a premature stop codon, and an amount of ofloxacin (e.g., paragraphs [0199]-[205], [0218], [0220]-[0226]).

Regarding claims 10-16, Wilde et al teach the administration of doses of the compounds from about 0.1 mg to about 2000 mg per day (e.g., paragraph [0224]).

Where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of the claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 U.S.C. 102, or "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). The present specification teaches that ofloxacin increases the expression of the ATM gene by acting on the promoter (e.g., paragraph [0037] and Tables 1 and 2). Because Wilde et al teach the administration of a compound to suppress a premature stop codon in combination with ofloxacin to a subject with ataxia telangiectasia, Wilde et al necessarily teach the administration of a compound to suppress a premature stop codon in the

ATM gene and ofloxacin, which will necessarily increase the expression of the ATM gene. Absent any evidence to the contrary, the doses taught by Wilde et al would be sufficient to enhance the production of functional protein by a factor of at least 30-fold relative to an untreated control, to enhance the production of functional protein by a factor of at least 3-fold relative to the production obtained using only the agent that suppresses the premature stop codon; and to enhance the level of functional protein to a level that corresponds to at least 10% of the level of functional protein generated from a corresponding native gene in which the premature stop codon is absent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-4 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilde et al (US Patent Application Publication No. 2004/0067900 A1, cited in a prior action; see the entire reference).

The teachings of Wilde et al are described above and applied as before. Wilde et al teach the use of compounds of Formula I and II as the nonsense suppressors (e.g., paragraphs [0015]-[0029]).

Wilde et al do not explicitly teach the use of gentamicin as the nonsense suppressor in the method of treating ataxia telangiectasia.

However, Wilde et al teach that the activity of the compounds of Formula I and II was determined relative to gentamicin, a small molecule known in the art to allow readthrough of premature termination codons (e.g., paragraph [0166]). Further, Wilde et al teach that gentamicin is an aminoglycoside antibiotic known to promote readthrough of eukaryotic stop codons and has therapeutic use in the treatment of human diseases caused by nonsense mutations (e.g., paragraphs [0010]-[0012]).

Wilde et al teach the administration of a compound of Formula I or II in combination with ofloxacin to treat ataxia telangiectasia. Because Wilde et al teach that the compound of Formula I or II is administered to promote readthrough of premature termination codons (e.g., paragraph [0029]), and Wilde et al teach that gentamicin is a compound known to promote readthrough of termination codons (e.g., paragraphs [0010]-[0012] and [0166]), it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute gentamicin for the compound of Formula I or II in order the achieve the predictable result of

providing a compound to treat ataxia telangiectasia that promotes readthrough of a nonsense codon.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Examiner
Art Unit 1636